ADHERENCE IN CLINICAL TRIALS
WHAT DO WE KNOW?

- ADHERENCE IS OFTEN HIGHER IN CLINICAL TRIALS DUE TO PARTICIPANT SELECTION AND VOLUNTARY STATUS
- LACK OF ADHERENCE SIGNIFICANTLY AFFECTS TRIAL RESULTS AND SAMPLE SIZE
- ADHERENCE IS MOST OFTEN PREDICTED IN FIRST MONTH OF TRIAL PARTICIPATION
- METHODS TO DETECT NON-ADHERENCE AND PROMOTE ADHERENCE MUST BE EMPLOYED PRIOR TO RANDOMIZATION AND MONITORED THROUGHOUT STUDY PARTICIPATION

ADHERENCE IN CLINICAL TRIALS
WHAT DO WE KNOW?

- NO SINGLE STRATEGY IS EFFECTIVE IN ENHANCING ADHERENCE. MULTIPLE COGNITIVE, BEHAVIORAL AND SOCIAL SUPPORT STRATEGIES IMPROVE ADHERENCE
- POTENTIAL DROP-OUTS CAN BE RECOVERED THROUGH A SERIES OF MANEUVERS
- STUDIES INVOLVING SELF-ADMINISTERED TREATMENTS SHOULD BE MEASURING ADHERENCE SO IT CAN BE TAKEN INTO ACCOUNT AS A CO-VARIATE

CLINICAL TRIALS: ENHANCING ADHERENCE INVOLVES A PLANNED APPROACH

- CONSIDER ADHERENCE IN STUDY DESIGN
- DEVELOP WRITTEN GUIDELINES FOR
  - APPROPRIATE PARTICIPANT SELECTION
  - PARTICIPATION AT CLINIC VISITS
  - MONITORING ADHERENCE TO STUDY REGIMENS INCLUDING COMPLETION OF STUDY QUESTIONNAIRES
  - STRATEGIES FOR MAINTAINING ADHERENCE DURING COURSE OF TRIAL
  - STRATEGIES FOR RETRIEVING "LOST" PARTICIPANTS
- EVALUATE STUDY ADHERENCE THROUGHOUT COURSE OF TRIAL THROUGH ONGOING MONITORING

FACTORS LIKELY TO IMPROVE ADHERENCE

STUDY DESIGN

- SHORTER STUDY DURATION
- CONTROLLED ENVIRONMENTS
- SIMPLICITY OF INTERVENTIONS

PARTICIPANT ENROLLMENT

- PT'S PERCEIVED BELIEF IN SUSCEPTIBILITY OR CONSEQUENCE OF CONDITION OR DISEASE
- PT'S PERCEIVED BENEFIT FROM INTERVENTION
- HIGHER LEVEL OF EDUCATION
- CLINIC SITE IN MULTI-CENTER STUDY
- *INFORMED PARTICIPANTS*

IS A RUN-IN ADVANTAGEOUS?

- USED SUCCESSFULLY IN MEDICATION TRIALS
- NORMALLY A MINIMAL PERFORMANCE IS >80% OF MEDICATION ADHERENCE
- RESULTS IN 5 TO 10% OF SUBJECTS BEING ELIMINATED
- MAY ADD TO COST, PERSONNEL
- TEST-DOSING IS AN ALTERNATIVE TO RUN-IN

U.S. PHYSICIANS HEALTH STUDY

- FACTORIAL DESIGN
- 6 MONTH RUN-IN – ASPIRIN AND BETA-CAROTENE
- 33,223 PHYSICIAN VOLUNTEERS
- 22,071 MET ADHERENCE CRITERIA
- ADHERENCE (RCT) 87.6% CONSUMING ONE MEDICATION AND 83.0% BOTH MEDICATIONS @ 57 MONTHS

STEERING COMMITTEE OF USPHS N ENG J MED 1989;321:129-135

PARTICIPANT EXCLUSION CRITERIA

TO IMPROVE ADHERENCE MOST OFTEN YOU EXCLUDE:

- THOSE ADDICTED TO DRUGS / ALCOHOL
- PERSONS LIVING TOO FAR (>30 – 60 MILES OF CLINIC)
- THOSE LIKELY TO MOVE DURING COURSE OF STUDY
- SEVERE MEDICAL PROBLEMS

INFORMING STUDY PARTICIPANTS
WHAT IS IMPORTANT?

- PT UNDERSTANDS CLINICAL TRIAL METHODOLOGY (BROCHURE, "INFORMATION FOR PATIENTS")
- PT IS ABLE TO REPEAT BACK TO YOU THEIR UNDERSTANDING OF TRIAL
- FAMILY MEMBERS ARE SUPPORTIVE
- PT IS PROVIDED A LISTING OF ALL FOLLOW–UP APPTS / CALLS
- CONTRACTS / WRITTEN AGREEMENTS ARE SIGNED
- A RELATIONSHIP IS FORMED WITH STUDY PERSONNEL (i.e. WARMTH, EMPATHY)
- CONTACT INFORMATION IS OBTAINED

WHAT SUPPORTS ON-GOING OPTIMAL ADHERENCE?

CLINIC-VISITS

- PRE-APPOINTMENT REMINDERS OR TELEPHONE PROMPTS (CONFIRMATION 24-48 HOURS)
- OFFERING INCENTIVES i.e. MILEAGE REIMBURSEMENT, FLEXIBLE APPT SCHEDULES, PARKING PASSES, CHILDCARE, TRANSPORTATION, HOME VISITS
- CONTINUED INVOLVEMENT OF "REGULAR" STAFF i.e. BUILDS TRUST, MAINTAINS FOLLOW-UP, OFFERS PROBLEM-SOLVING

NATIONAL BETA-BLOCKER HEART ATTACK TRIAL

	PROPRANOLOL		PLACEBO	
YEAR	NUMBER OF VISITS REQUIRED	PERCENT OF VISITS COMPLETED*	NUMBER OF VISITS REQUIRED	PERCENT OF VISITS COMPLETED*
1ST YEAR	11,176	94.5	11,034	94.7
2ND YEAR	5,325	93.5	5,197	92.3
3RD YEAR	1,873	93.4	1,835	91.1
TOTAL	18,374	94.1	18,066	93.6

*INCLUDES INTERVIEWS WITHOUT EXAMINATIONS

BELL, RL et al. CONTROLLED CLIN TRIALS 6:89-101, 1985.

WHAT KEEPS PARTICIPANTS INVOLVED?

IN-BETWEEN CONTACTS

- WELCOME PACKETS WITH PERSONNEL NAMES AND CONTACT NUMBERS
- BIRTHDAY AND HOLIDAY CARDS
- MULTI-SITE NEWSLETTERS
- CARDS FOR HOSPITALIZED PARTICIPANTS
- INCENTIVES (i.e. CPR COURSE)

DROPOUTS (%) AT FIRST AND LAST VISITS POSTRANDOMIZATION IN LONG-TERM STUDIES

STUDY	% DROPOUTS	TIME OF VISITS
BHAT	3.5, 15	1 MO., 36 MO.
AMIS	3, 6	1 MO., 36 MO.
U.K. PHYSICIANS	18, 30	6 MO., 72 MO.
CAPS	4, 9	3 MO., 12 MO.
LRC CPPT	1, 1.8, 6.1	2 WKS, 4 WKS, 7.4 YRS
B-MC*	2, 4, 0.6	2 WKS, 4 WKS, 7.4 YRS

AMIS = ASPIRIN MYOCARDIAL INFARCTION STUDY; BHAT = BETA-BLOCKER HEART ATTACK TRIAL; CAPS = CARDIAC ARRHYTHMIA PILOT STUDY; LRC-CPPT = LIPID RESEARCH CLINIC'S CORONARY PRIMARY PREVENTION TRIAL; UK PHYSICIANS = UNITED KINGDOM PHYSICIANS TRIAL OF PROPHYLACTIC ASPIRIN FOR CARDIOVASCULAR DISEASE MORTALITY.

PROBSTFIELD JL, et al. DROPOUTS FROM A CLINICAL TRIAL, THEIR RECOVERY AND CHARACTERIZATION: A BASIS FOR DROPOUT MANAGEMENT AND PREVENTION. IN: SHUMAKER SA, SHRON EB, OCKENE JK (ED): THE HANDBOOK OF HEALTH BEHAVIOR CHANGE. NEW YORK: SPRINGER; 1990: 376-400.

RECOVERING DROPOUTS: SPECIFIC APPROACH

- COMPUTER-BASED SURVEILLANCE SYSTEM FOR MONITORING ADHERENCE
- SIX BASIC PRINCIPLES FOR COUNSELING
- PROCEDURES FOR REINSTITUTION OF PROTOCOL DURING DROPOUT RECOVERY

PROBTFIELD JL, et al. AM J MED 80:777-784, 1989.

ANTIHYPERTENSIVE AND LIPID LOWERING TREATMENT TO PREVENT HEART ATTACK (ALLHAT)

SPONSORED BY NHLBI AND DEPARTMENT OF VETERAN'S AFFAIRS

RANDOMIZED PRACTICE-BASED TRIAL IN 42,500 HIGH RISK HYPERTENSIVE PATIENTS (55 YRS+) – 600 CENTERS

ANTIHYPERTENSIVE AND LIPID LOWERING TREATMENT TO PREVENT HEART ATTACK (ALLHAT)

HTN COMPONENT – DOUBLE–BLIND DESIGN TO DETERMINE WHETHER COMBINED INCIDENCE OF FATAL CHD AND NON–FATAL MI DIFFER BETWEEN DIURETIC (CHLORTHALIDONE) AND 3 OTHERS – AMLODIPINE, LISINOPRIL OR DOXAZOSIN

LL COMPONENT – OPEN–LABEL TRIAL (20,000) IN MODERATELY HYPERCHOLESTEROLEMIC MEN AND WOMEN (55 YRS+) WITH PRAVASTATIN WILL REDUCE ALL–CAUSE MORTALITY AS COMPARED TO USUAL CARE

WHAT'S IMPORTANT IN MONITORING ADHERENCE TO STUDY REGIMENS?

- NO SINGLE MEASURE OF ADHERENCE GIVES YOU A COMPLETE PICTURE
- NO WIDELY ACCEPTED DEFINITION OR CRITERION EXISTS FOR EITHER GOOD OR POOR ADHERENCE

FRIEDMAN LM et al. FUNDAMENTALS OF CLINICAL TRIALS 1998.

HINT:

ALWAYS ANTICIPATE WHAT THE REVIEWER WILL WANT TO KNOW WHEN YOUR TRIAL IS PUBLISHED. CAN YOU DEVELOP THE TABLES?

MONITORING ADHERENCE TO STUDY REGIMENS

- FREQUENCY OF FOLLOW-UP VISITS / CONTACTS
- COMPLETION OF STUDY QUESTIONNAIRES (i.e. LOGS, CALENDARS, BASELINE, FOLLOW-UP)

MEDICATION TRIALS

- PILL COUNTS
- MEDICATION-TAKING BEHAVIORS
  - CHANGE IN DOSAGES, SIDE EFFECTS
  - REASON FOR CHANGE IN MEDS
- LABORATORY MEASURES
  - MARKERS, URINE ASSAYS
- MEDICATION EVENT MONITORS

MONITORING ADHERENCE TO STUDY REGIMENS

BEHAVIORAL TRIALS

- INTERVIEWS / RECORDS
  - DIET – 24 HOURS RECALL / 7 DAY FOOD RECORDS
  - EXERCISE – CALENDARS/LOGS – FREQENCY & INTENSITY OF EXERCISE
  - SYMPTOMS – FREQ. OF ANGINA / NITROGLYCERIN

FACTORS AFFECTING ADHERENCE IN SPECIAL POPULATIONS

ELDERLY

- COGNITIVIE FUNCTIONING
- POLY PHARMACY, DRUG/DRUG INTERACTIONS
- LIVING ALONE
- TRANSPORTATION
- LENGTH OF VISITS

ETHNIC POPULATIONS

- SOCIAL STRUCTURE
- CULTURAL BELIEFS
- LITERACY